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Efficient synthesis of 3-hydroxymethylated *cis*- and *trans*-cyclobutane β -amino acids using an intramolecular photocycloaddition strategy

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Abstract

Uracil bearing a tethered allyl alcohol appendage at N1 undergoes a [2+2] photocycloaddition reaction to provide a single tricyclic adduct in high yield. This compound is transformed in one step into a *cis*-cyclobutane β -amino acid bearing a 3-hydroxymethyl group. Through appropriate functionalization and epimerization, the *trans* isomer is obtained therefrom in only three further steps.

1. Introduction

β -Amino acids, and the various peptide structures which include them, often possess interesting structural and biological properties which are complementary to those of their more abundant α -amino acid congeners.¹ The controlled preparation of β -amino acids is therefore of considerable importance for synthetic chemists.² Since a significant part of the interest in these compounds derives from their ability to adopt and impose marked conformational preferences, there has been a particular focus on alicyclic β -amino acids and peptide derivatives thereof.^{3,4} Thus, synthetic efforts have been devoted to derivatives of cyclohexane,⁵ cyclopentane,⁶ and cyclopropane⁷ β -amino acids, although a number of more elaborate carbocyclic scaffolds have also been studied.⁸

Cyclobutane β -amino acids—more formally, 2-amino-1-cyclobutanecarboxylic acids (ACBAs) optionally bearing

ring substituents—should clearly play a significant role in this field, but until now very little study has been made of these carbocycles.^{9,10} This can be partly explained by the paucity of convenient synthetic methods giving access to these building blocks. Only a few synthetic strategies for the preparation of ACBAs have been disclosed. Kennewell et al.¹¹ showed that *meso*-1,2-cyclobutanedicarboxylic acid derivatives could be desymmetrized with one of the functions being transformed into an amine, thus providing access to racemic *cis*-ACBA. Two enantioselective versions of this approach have been described, by the groups of Ortu o et al.¹² and Bolm et al.¹³ Until very recently, only racemic syntheses of *trans*-ACBA had been described, via analogous desymmetrization of the racemic *trans*-diacid.^{11,14}

Ring-substituted ACBAs are rare, and the available synthetic methods lack selectivity and/or generality. ACBAs bearing simple hydrocarbon moieties (alkyl, phenyl, and methylene) at the C3 and/or C4 position have been described,^{6c,15} while a novel acyl nitrene insertion reaction has provided an isolated entry to 3-hydroxy-ACBAs.¹⁶ In earlier work, Brannock et al.¹⁷ prepared a series of *N,N*-dialkylated 3,3-dialkyl-ACBA esters via a thermal [2+2] cycloaddition

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between enamines and acrylates, although these reactions required harsh conditions and were bereft of stereoselectivity. This approach for the construction of ACBAs has been adapted to give related derivatives, usually under milder conditions.¹⁸ Interestingly, fully functionalized derivatives of 4-hydroxymethylated *cis*- and *trans*-ACBA have been prepared via photopyridones.¹⁹

We recently demonstrated the utility of a [2+2] photocycloaddition reaction between uracil and ethylene as a rapid and simple entry to *cis*-ACBA.²⁰ Use of a chiral uracil derivative provided access to enantiomerically pure materials,²¹ and these were epimerized in a five-step procedure to establish the first access to *trans*-ACBA in enantiomerically pure form.^{21a} In an extension of this photochemical approach, using a series of 5- or 6-substituted uracils, the corresponding 1- and 2-substituted *cis*-ACBAs were prepared,²² including the 1-hydroxymethylated compound.

We wished to further extend this methodology to the preparation of the hitherto unknown 3-hydroxymethyl-ACBA. The particular interest of the primary alcohol substituent lies in its wide potential for grafting of (or transformation into) other side chain entities. In intermolecular [2+2] photocycloadditions with unsymmetrical partners, the possibility of the formation of regioisomers and stereoisomers arises, and in many cases product mixtures are formed.²³ An intramolecular process is generally much more selective, and indeed a few examples have been described, which involve uracil derivatives.²⁴ In consequence, we decided to investigate the reactivity of a uracil bearing a cleavable tether at N1, which would deliver the equivalent of allyl alcohol in an intramolecular fashion (Fig. 1).

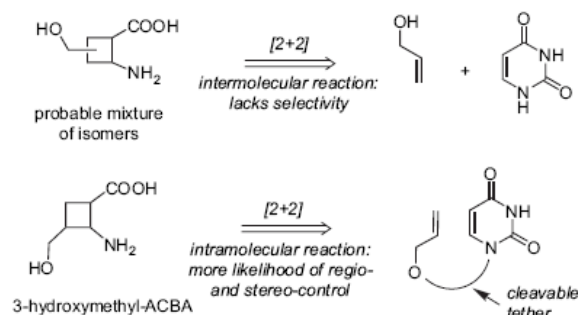


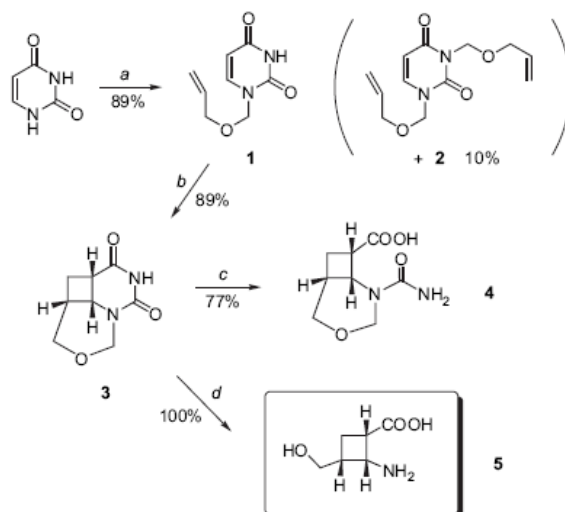
Figure 1. Retrosynthetic analysis.

2. Results and discussion

2.1. Preparation of the *cis*-cyclobutane β -amino acid

We selected to study 1-(allyloxymethyl)uracil **1**. This compound, first described by Ozerov et al.,²⁵ was conveniently prepared by selective N1-alkylation of uracil using chloromethyl allyl ether²⁶ in the presence of cesium iodide and *N,O*-bistrimethylsilylacetamide (BSA) in an adaptation of Pederson's procedure²⁷ (Scheme 1). A small amount of the

N1,N3-dialkylated material **2** was the only by-product, and was easily separated by filtration.



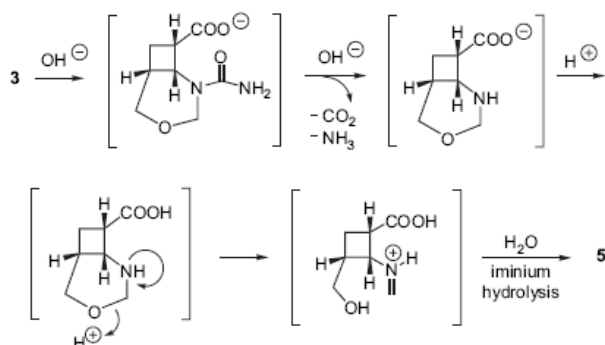
Scheme 1. Reagents and conditions: (a) $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{Cl}$, BSA, CsI, CH_2Cl_2 rt, 4 h. (b) $h\nu$, acetone, Pyrex, rt, 4 h. (c) 0.5 M NaOH, rt, 18 h. (d) 1 M NaOH, 80 °C, 10 h, then 1 M HCl.

Compound **1** was subjected to [2+2] photocycloaddition reaction conditions (Scheme 1). A solution of **1** in acetone was irradiated with a 400 W medium-pressure Hg vapor lamp fitted with a Pyrex filter under argon for 4 h. In these conditions, the tricyclic cyclobutane adduct **3** was obtained as a single product in 89% isolated yield.²⁸ In alternative reaction conditions, using a quartz reaction vessel and acetonitrile as the solvent, **3** was produced along with several by-products and its isolated yield was lower (66%). The structure of compound **3** was determined by 1D and 2D NMR experiments. The relative stereochemistry was attributed by comparison of NMR spectral data with those of related compounds^{24a} and supported by NOE observations. An all-*cis* configuration was thus assigned for **3**, which had therefore been formed with complete regio- and stereo-chemical selectivities.

Next, the controlled degradation of the heterocyclic rings was undertaken. It was hoped that subjecting **3** to acidic conditions would induce oxazine ring opening via an intermediate *N*-acyl iminium, which might then be hydrolyzed.²⁹ In the event, treatment of **3** with TFA or HCl yielded only unreacted starting material. Other attempts to open the oxazine ring of **3** using TMSI³⁰ or BBr_3 ³¹ also failed.

We therefore turned our attention to the dihydrouracil ring. Our recent work on cyclobutane dihydrouracil adducts had shown that treatment with NaOH in mild conditions can effect selective N3–C4 bond cleavage to provide the corresponding cyclobutane β -urea acids.^{20–22} Indeed, overnight treatment of **3** with 0.5 M NaOH (6 equiv) at room temperature furnished compound **4** in 77% yield (Scheme 1). Previously, it had been noted that in more strongly basic conditions, dihydrouracils can be converted directly into β -amino acids.³² This appeared a more attractive prospect, since we felt that removal of

the acyl group from the nitrogen atom should make acid-mediated oxazine ring opening easier. In the event, treatment of **3** with a 1 M solution of NaOH at 80 °C for 10 h followed by neutralization and passage through acidic anion exchange resin led *directly* to the target cyclobutane β -amino acid **5** in quantitative yield (Scheme 1). The probable sequence of events for this last step is presented in Scheme 2.



Scheme 2. Proposed sequence of events in the transformation of **3** into **5**.

The new *cis*-cyclobutane β -amino acid **5** was thus obtained in a very efficient and selective three-step process from uracil (79% overall yield). It was of interest to note that **5** was only moderately stable in aqueous solution, degrading over a period of hours at room temperature. A similar phenomenon has been observed for the parent β -amino acid and can be imputed to an irreversible ‘push-pull’ induced ring opening process.³³

2.2. Preparation of the *trans*-cyclobutane β -amino acid

With the *cis*- β -amino acid **5** in hand, we next investigated its controlled epimerization at C1 in order to gain entry to the *trans* isomer (Scheme 3). Initially, protection of the amine function of **5** was necessary in order to suppress material loss through the ring opening phenomenon. Treatment of **5** with Boc_2O in standard conditions gave the *tert*-butyl carbamate **6** in only moderate yield (45%), presumably due to the steric congestion around the nitrogen atom of the all-*cis* cyclobutane skeleton. The use of 9-fluorenylmethylsuccinimidyl carbonate

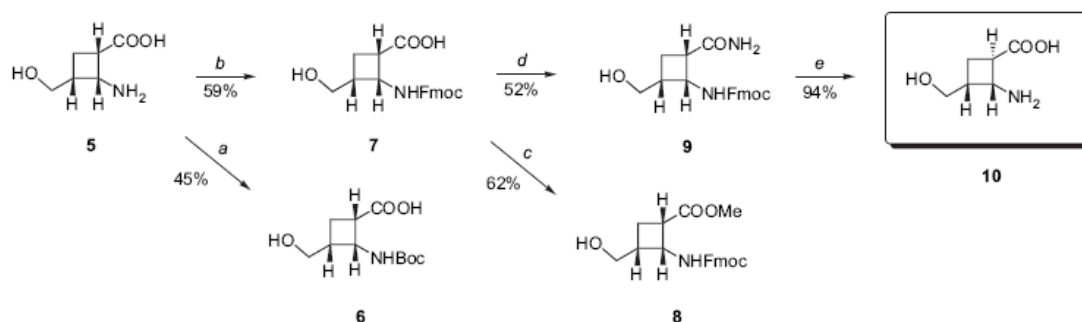
(FmocONSu) in the presence of NaHCO_3 furnished the required *N*-protected amino acid **7** in 59% yield. FmocONSu was a superior reagent to FmocCl, which provided **7** in only 13% yield.

We were able to prepare the methyl ester **8** (62% yield) from **7** in standard acidic conditions ($\text{MeOH}/\text{H}_2\text{SO}_4$) without inducing lactonization, leaving the primary alcohol as the only free functional group. The carboxamide **9** was also prepared (52% yield) by treatment of **7** with NH_4HCO_3 in the presence of Boc_2O and pyridine.³⁴

We have recently studied the base-mediated *cis* to *trans* C1 epimerization of the parent (i.e., bearing no other ring substituents) cyclobutane β -amino acid, in both methyl ester^{21a} and carboxamide³⁵ derivatized forms. The latter was arguably more efficient, so we applied the appropriate epimerization conditions to carboxamide **9**. Treatment of this compound with 25% aqueous NaOH solution in refluxing methanol provided the *trans*- β -amino acid **10** *directly*, in 94% yield (Scheme 3). This final transformation is achieved via three consecutive steps: Fmoc group cleavage, *cis* to *trans* epimerization of the intermediate carboxamide, and then hydrolysis of carboxamide to carboxylic acid. The stability of the *trans*-cyclobutane β -amino acid product in the vigorous reaction conditions is noteworthy, and the absence of any products with a *cis* configuration is remarkable. The three-step *cis* to *trans* epimerization procedure (starting and finishing with free β -amino acid functions) is the shortest such sequence of which we are aware.

3. Conclusion

In conclusion, the intramolecular version of the uracil–olefin [2+2] photocycloaddition methodology provides a short and efficient entry to 3-hydroxylated *cis*-cyclobutane β -amino acid, which can be transformed into the *trans* isomer via selective functionalization and an efficient multi-step epimerization process. These procedures are expected to be of use for the preparation of β -peptides bearing multiple and varied side chain appendages, through further derivatization of the primary alcohol moieties. Work in this respect is in progress.



Scheme 3. Reagents and conditions: (a) Boc_2O , NaOH, dioxane/ H_2O , 0 °C to rt, 2.5 h. (b) FmocONSu, NaHCO_3 , acetone/ H_2O , rt, 16 h. (c) MeOH , H_2SO_4 (cat), –15 °C, 16 h. (d) Boc_2O , NH_4HCO_3 , pyridine, dioxane, rt, 5 h. (e) 25% aq NaOH, MeOH , Δ , 3 h.

4. Experimental

4.1. General methods

Melting points were obtained on a Reichert microscope apparatus. Elemental analyses were performed on a Thermo-finnigan EA 1112 instrument. IR spectra were recorded on a Perkin–Elmer Aragon 500 spectrometer; only diagnostic absorbances (ν_{\max}) are given. NMR spectra were recorded on a Bruker AC-400 spectrometer operating at 400 MHz (^1H) or 100 MHz (^{13}C); chemical shifts (δ) are reported in parts per million, J values are given in hertz. MS data were obtained in CI mode (150 eV; vector gas: CH_4) on a Hewlett–Packard 5989B instrument, or in positive ESI mode (3000 V) on a Waters micro Q-TOF instrument.

Flash chromatography was carried out on columns of silica gel (40–63 μm); the appropriate eluent is indicated in parentheses. Isolation of amino acids was carried out on columns of Dowex 50X8 ion exchange resin (50–100 mesh) in H^+ form.

4.1.1. 1-(Allyloxymethyl)uracil (**1**)

Uracil (3.13 g, 28 mmol) was added to a solution of *N,O*-bistrimethylsilylacetamide (19.7 g, 97 mmol) in CH_2Cl_2 (280 mL) under argon. The reaction mixture was stirred for 10 min then chloromethyl allyl ether²⁶ (4.50 g, 42 mmol) and cesium iodide (7.20 g, 28 mmol) were added. The reaction mixture was stirred at rt for 4 h. The mixture was washed with saturated aqueous Na_2CO_3 solution (200 mL) and then extracted with CH_2Cl_2 (3 \times 150 mL). The combined organic layers were dried over MgSO_4 , filtered, and then evaporated to yield a yellow powder. This residue was triturated with EtOAc and filtered to give compound **1** as a white powder (4.55 g, 89%). Mp 117–118 °C; IR (KBr) ν_{\max} 1732, 1681, 1828 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.28 (s, 1H), 7.32 (d, 1H, $J=8$ Hz), 5.80–5.95 (m, 1H), 5.77 (d, 1H, $J=8$ Hz), 5.22 (d, 2H, $J=10$ Hz), 5.17 (s, 2H), 4.09 (s, 2H); ^{13}C NMR (CDCl_3) δ 163.8, 151.2, 143.2, 133.1, 118.4, 103.2, 76.0, 70.5; MS (CI) m/z 183 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.76; H, 5.59; N, 15.26.

The filtrate was evaporated and the residue was purified by flash chromatography (EtOAc) to furnish **2** as a colorless oil (0.70 g, 10%). IR (CCl_4) ν_{\max} 1730, 1680, 1629 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.30 (d, 1H, $J=8$ Hz), 5.80–5.95 (m, 2H), 5.77 (d, 1H, $J=8$ Hz), 5.22 (d, 4H, $J=10$ Hz), 5.20 (s, 2H), 5.17 (s, 2H), 4.10 (s, 2H), 4.08 (s, 2H); ^{13}C NMR (CDCl_3) δ 163.8, 151.3, 143.3, 133.2, 118.4, 118.2, 103.4, 103.2, 76.0, 75.9, 70.8, 70.5; MS (CI) m/z 253 $[\text{M}+\text{H}]^+$.

4.1.2. 1,3-Diaza-9-oxa-2,4-dioxatricyclo[5.3.1.0^{5,11}]-undecane (**3**)

A solution of **1** (1.00 g, 5.5 mmol) in acetone (510 mL) was irradiated under argon for 4 h at rt in an annular reactor equipped with a water cooling system using a 400 W medium-pressure Hg vapor lamp fitted with a Pyrex filter. The solvent was then evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 3:7) to give **3** as a white powder (0.89 g, 89%). Mp 167–168 °C; IR (KBr) ν_{\max}

1694 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.71 (d, 1H, $J=11$ Hz), 4.23 (q, 1H, $J=4$ Hz), 4.13 (d, 1H, $J=11$ Hz), 3.56 (d, 2H, $J=7$ Hz), 3.22 (m, 2H), 2.66 (m, 1H), 2.57 (q, 1H, $J=10$ Hz), 2.44 (m, 1H); ^{13}C NMR (CDCl_3) δ 173.8, 153.1, 71.2, 67.0, 51.2, 33.6, 31.6, 27.2; MS (CI) m/z 183 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.37; H, 5.61; N, 14.97.

4.1.3. 2-Carbamoyl-2-aza-4-oxabicyclo[4.2.0]octane-8-carboxylic acid (**4**)

A solution of **3** (0.65 g, 3.6 mmol) in 0.5 M aqueous NaOH (23 mL) was stirred at rt overnight. Cation exchange resin (Bio-Rad AG 50W-X8, H^+ , 20–50 mesh) was then added until pH=4–5. Filtration and then evaporation of the filtrate left **4** as yellow crystals (0.55 g, 77%). Mp 142–143 °C; IR (KBr) ν_{\max} 3550, 3400, 1700, 1660 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 12.09 (s, 1H), 6.00 (br s, 2H), 5.02 (d, 1H, $J=8$ Hz), 4.53 (t, 1H, $J=9$ Hz), 4.45 (d, 1H, $J=8$ Hz), 3.95 (dd, 1H, $J=9$ and 11 Hz), 3.68 (dd, 1H, $J=10$ and 8 Hz), 3.40 (m, 1H), 2.72 (m, 1H), 1.96 (m, 2H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 174.6, 156.8, 74.0, 68.8, 47.0, 42.2, 31.0, 21.9. HRMS (ESI) Calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: m/z 223.1817; found 223.1695.

4.1.4. *cis*-2-Amino-3-hydroxymethyl-1-cyclobutane-carboxylic acid (**5**)

A solution of **3** (1.00 g, 5.5 mmol) in 1 M aqueous NaOH (40 mL) was stirred at 80 °C for 10 h. After cooling, the solution was acidified with 1 M HCl (35 mL) and then loaded onto a column of ion exchange resin. Elution with 1 M NH_4OH solution afforded **5** as yellow crystals (0.80 g, 100%). Mp 153–154 °C; IR (KBr) ν_{\max} 3360 (br), 1710 cm^{-1} ; ^1H NMR (D_2O) δ 3.98 (t, 1H, $J=8$ Hz), 3.69 (d, 2H, $J=7$ Hz), 3.21 (q, 1H, $J=9$ Hz), 2.73 (q, 1H, $J=8$ Hz), 2.28 (q, 1H, $J=8$ Hz), 1.93 (q, 1H, $J=8$ Hz); ^{13}C NMR (D_2O) δ 180.1, 60.2, 48.9, 38.2, 35.2, 24.7. Anal. Calcd for $\text{C}_6\text{H}_{11}\text{NO}_3\cdot\text{H}_2\text{O}$: C, 44.17; H, 8.03; N, 8.58. Found: C, 43.67; H, 7.68; N, 8.95.

4.1.5. *cis*-2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxymethyl-1-cyclobutanecarboxylic acid (**6**)

To a solution of **5** (0.20 g, 1.7 mmol) in a mixture of dioxane (2 mL) and 1 M aqueous NaOH (1 mL) was added di-*tert*-butyl dicarbonate (0.38 g, 1.7 mmol). The mixture was stirred at rt for 2.5 h and then evaporated. Water (1.6 mL) was added and the solution was acidified with 1 M HCl until pH=2–3. The mixture was extracted with EtOAc (3 \times 7 mL) and combined organic layers were dried over MgSO_4 , filtered, and then evaporated to give **6** as a greenish oil (0.15 g, 45%). IR (CCl_4) ν_{\max} 3360 (br), 1740, 1710 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.25 (s, 1H), 4.42 (s, 1H), 4.23 (t, 1H, $J=7$ Hz), 3.94 (dd, 2H), 3.43 (m, 1H), 2.92 (m, 1H), 2.56 (m, 2H), 2.15 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (CDCl_3) δ 175.6, 156.1, 84.2, 60.0, 48.4, 37.5, 35.5, 26.6, 22.5.

4.1.6. *cis*-2-*N*-(9-Fluorenylmethyloxycarbonyl)amino-3-hydroxymethyl-1-cyclobutanecarboxylic acid (**7**)

To a solution of **5** (0.10 g, 0.7 mmol) and NaHCO_3 (0.12 g, 1.4 mmol) in a mixture of water (7 mL) and acetone (7 mL)

was added 9-fluorenylmethylsuccinimidyl carbonate (FmocONSu) (0.40 g, 1.2 mmol). The mixture was stirred at rt for 16 h and then acetone was evaporated carefully under reduced pressure. Excess FmocONSu was removed by extraction with EtOAc (3×10 mL). The residual aqueous layer was acidified with 1 M HCl until pH=1–2 and then extracted with CH₂Cl₂ (3×10 mL). Combined organic layers were dried over MgSO₄, filtered, and then evaporated to give **7** as white crystals (0.15 g, 59%). Mp 38–39 °C; IR (KBr) ν_{max} 3360, 1740, 1710 cm⁻¹; ¹H NMR (CDCl₃) δ 7.75 (d, 2H, *J*=8 Hz), 7.56 (d, 2H, *J*=8 Hz), 7.38 (t, 2H, *J*=8 Hz), 7.29 (t, 2H, *J*=8 Hz), 6.60 (d, 1H, *J*=6 Hz), 4.67 (q, 1H, *J*=8 Hz), 4.41 (m, 2H), 4.19 (t, 1H, *J*=8 Hz), 3.70 (m, 2H), 3.48 (q, 1H, *J*=8 Hz), 2.80 (m, 1H), 2.65 (s, 1H), 2.15 (m, 2H); ¹³C NMR (CDCl₃) δ 176.6, 157.2, 143.7, 141.25, 127.7, 127.1, 125.2, 120.0, 67.3, 61.35, 49.2, 47.1, 39.9, 39.5, 22.9; MS (ESI) *m/z* 390 [M+Na]⁺. Anal. Calcd for C₂₁H₂₁NO₅: C, 67.65; H, 5.76; N, 3.81. Found: C, 67.45; H, 5.95; N, 3.78.

4.1.7. Methyl *cis*-2-*N*-(9-fluorenylmethyloxycarbonyl)-amino-3-hydroxymethyl-1-cyclobutanecarboxylate (**8**)

A solution of **7** (0.05 g, 0.14 mmol) in MeOH (0.33 mL) was cooled to -15 °C and 95% H₂SO₄ (4 μ l) was added slowly. The mixture was stirred at -15 °C for 16 h, warmed to 0 °C, and neutralized by slow addition of a saturated aqueous NaHCO₃ solution over 1 h. After removal of solids by filtration, the filtrate was evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 6:4) to give **8** as a white powder (0.03 g, 62%). Mp 85–86 °C; IR (KBr) ν_{max} 3390, 2960, 1725, 1520 cm⁻¹; ¹H NMR (CDCl₃) δ 7.77 (d, 2H, *J*=8 Hz), 7.61 (d, 2H, *J*=8 Hz), 7.39 (t, 2H, *J*=8 Hz), 7.31 (t, 2H, *J*=8 Hz), 6.55 (d, 1H, *J*=6 Hz), 4.61 (q, 1H, *J*=8 Hz), 4.37 (m, 2H), 4.21 (t, 1H, *J*=7 Hz), 3.70 (s, 1H), 3.60 (m, 2H), 3.47 (q, 1H, *J*=8 Hz), 2.92 (m, 1H), 2.79 (s, 1H), 2.20 (m, 2H); ¹³C NMR (CDCl₃) δ 173.8, 156.9, 143.9, 141.3, 127.7, 127.1, 125.1, 120.0, 67.2, 61.5, 52.0, 49.6, 47.2, 46.8, 39.6, 23.2; MS (ESI) *m/z* 404 [M+Na]⁺. Anal. Calcd for C₂₂H₂₃NO₅: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.52; H, 5.60; N, 3.42.

4.1.8. *cis*-2-*N*-(9-Fluorenylmethyloxycarbonyl)amino-3-hydroxymethyl-1-cyclobutanecarboxamide (**9**)

To a solution of **7** (0.07 g, 0.19 mmol) in dioxane (4 mL) were added di-*tert*-butyl dicarbonate (0.06 g, 0.27 mmol), ammonium hydrogen carbonate (0.05 g, 0.57 mmol), and pyridine (0.03 g, 0.38 mmol). The mixture was stirred at rt for 5 h and then water (3 mL) was added. This mixture was extracted with EtOAc (3×3 mL) and combined organic layers were dried over MgSO₄, filtered, and then evaporated. The residue was purified by flash chromatography (cyclohexane/EtOAc 6:4) to give **9** as a yellow oil (0.04 g, 52%). IR (CCl₄) ν_{max} 3360, 1740, 1700 cm⁻¹; ¹H NMR (CDCl₃) δ 7.76 (d, 2H, *J*=8 Hz), 7.57 (d, 2H, *J*=8 Hz), 7.40 (t, 2H, *J*=8 Hz), 7.31 (t, 2H, *J*=8 Hz), 5.40 (d, 1H, *J*=6 Hz), 5.08 (m, 1H), 4.58 (m, 1H), 4.46 (m, 3H), 4.41 (d, 2H, *J*=6 Hz), 4.19 (t, 1H, *J*=7 Hz), 3.26 (m, 1H), 2.93 (m, 1H), 2.03 (m, 1H), 1.73 (m, 1H); ¹³C NMR (CDCl₃) δ 172.2, 155.5, 143.6,

141.2, 127.7, 127.0, 124.9, 119.9, 68.3, 67.0, 47.0, 46.9, 46.8, 38.3, 23.0.

4.1.9. *trans*-2-Amino-3-hydroxymethyl-1-cyclobutanecarboxylic acid (**10**)

To a stirred solution of **9** (0.04 g, 0.09 mmol) in MeOH (1 mL) was added 25% aqueous NaOH (5 mL, 6.3 mmol). The mixture was stirred at reflux for 3 h, MeOH was evaporated carefully under reduced pressure, and the residual aqueous phase was extracted with CH₂Cl₂ (3×5 mL). The aqueous layer was then neutralized at -5 °C with 1 M HCl and then loaded onto a column of ion exchange resin. Elution with 1 M NH₄OH solution afforded **10** as yellow crystals (0.01 g, 94%). Mp 172–173 °C; IR (KBr) ν_{max} 3360, 1710 cm⁻¹; ¹H NMR (D₂O) δ 3.72 (m, 2H), 3.56 (m, 2H), 3.10 (q, 1H, *J*=8 Hz), 2.50 (m, 1H), 2.07 (q, 1H, *J*=9 Hz), 1.96 (q, 1H, *J*=10 Hz); ¹³C NMR (D₂O) δ 173.8, 60.9, 50.6, 43.0, 35.8, 24.8.

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